SPECIFICATION

PAD BASE FOR ENDERMISM AND INJECTION NEEDLE

TECHNICAL FIELD

The present invention relates to a pad base for endermism used when percutaneously administrating a drug which acts on organism *in vivo* and an injection needle. The pad base is a portion assuming the percutaneous administration of a drug in a pad for percutaneous medication. The pad for percutaneous medication is an article covering the pad base with, for example, a pressure-sensitive adhesive sheet from the reverse of the skin side, and the like. When the pad base for endermism is used, the pad base side is pasted on the skin.

BACKGROUND ART

The skin functions as a barrier for protecting the body and inhibits the invasion of a foreign substance in organism. Specifically, the stratum corneum of the outermost layer which is directly brought in contact with the foreign substance assumes the great role as a barrier. To be sure, although the digestive tract is the same as the skin from the viewpoint of being directly brought in contact with the foreign substance, the digestive tract has no barrier of stratum corneum such as the skin, and it is rather composed of the nutritional absorptive cell having function positively taking in nutritional components from the foreign substance, namely foods. Both the skin and the digestive tract differ from each other greatly in this point.

On the other hand, the skin also has a function (a function of insensible perspiration) of discharging, and can be considered not as a simple protective membrane but an organ having adjusting function of permeating substances.

By the way, intramuscular injection, oral administration and administration from the colon by a suppository have been known as the administration procedure of a drug to organism. A percutaneous absorption method of administrating from the skin has been proposed focusing attention on the above-mentioned function of the skin. According to the percutaneous absorption method, the administration is nearly indolent, the control of medication is easy, adverse reaction is hardly generated, and it is expected that the QOL (Quality Of Life) of a subject is also remarkably improved because of the convenience of administration mode. Further, isosorbide dinitrate, estradiol, tulobuterol, nicotine, clonidine, scopolamine, fentanyl, lidocaine and the like in addition to nitroglycerine have been developed as percutaneously absorptive type pharmaceuticals.

The above-mentioned percutaneously absorptive type pharmaceuticals has advanced the study of percutaneous absorption of a drug and it has been clear that there were many drugs which could not be percutaneously absorbed by any method in accordance with the proceeding.

Then, a method of instantaneously perforating extremely fine pores in the skin and introducing a drug utilizing the procedure of Electroporation which is used for introducing gene in cells; a method of Iontophoresis which introduces into the skin an ionized drug using the technique of electrophoresis; or an administration method combining these have been

devised as the percutaneous absorption method next generation instead of the procedure of simply diffusing and absorbing a drug from the stratum corneum into the skin in conventional methods.

As a means for perforating fine pores in the skin in like manner as the Electroporation, a MicroPatch method of bringing a pad with numerous tiny needles in contact with the skin and injecting a drug from the stinging needles site has been proposed.

To illustrate the MicroPatch method more specifically, a pad for endermism used in the MicroPatch method is equipped with a plural number of solid-core thick and short needles (made of silicon, a metal, or a plastic) with acicular pyramids of 10 to 50 μm and a reservoir for drug solution. When it is used, the above-mentioned needles sting the skin, gaps are broadened by vibrating the contact plane of the needles with the skin by a vibrator (100 MHz to 2000 MHz), and the drug solution from the above-mentioned reservoir is designed to be invaded into the skin from the extremely fine pore spots of the skin (for example, refer to U.S.P. No. 6,183,434).

As the drug administered by the MicroPatch method, insulin, morphine, α-interferon, parthyroid hormone, erythropoietin and the like are developed (Altea Therpeutics Inc., Atlanta, USA), insulin and the like have been already under the first phase of clinical test and studies for practical application are proceeding.

As the administration method, a non needle injection method which is in contrast to the above-mentioned method is also proposed. Concretely, a method of administrating subcutaneously under pressuring an injection

solution, or a method of using gas with high pressure by which the powder of a drug is subcutaneously beaten in under high pressure, or the like are proposed. Practically, a portion of them is already commercialized.

Although these administration methods have both merits and demerits, the MicroPatch method is a superior method from the viewpoints that it does not require specific devices and any one can easily use it.

DISCLOSURE OF THE INVENTION

The reason why a thick needle is used in a conventional MicroPatch method as described above is that if a long thin minute needle is used, it may fracture easily and remain in the skin, and there is a there is a fear that bad influence to organism. On the other hand, administration by vibration is essential for a procedure using a thick short needle, as described above. Accordingly, the permeation of a drug in the skin is dependent on the presence or absence of vibration, therefore a power source and the like are essential for administration of a drug.

A thin needle is desired for mitigating pain in a usual injection needle, but when it is too thin, there is a fear of fracturing, and if it fractures, there is a fear that it remains in the skin and badly influences an organism.

Consequently, the present invention has been performed under the above-mentioned circumstances, and the object is to provide a pad base for endermism hardly exercising bad influence on organism even if a needle fractures and remains in the skin in the MicroPatch method. Further, the object is to provide a pad base for endermism hardly exercising bad influence on organism even if a needle fractures and remains in the skin in case of a

usual injection needle.

The pad base for endermism of the present invention is characterized by a pad base for endermism comprising a minute needle installed upright on the skin side of a patch base for skin, wherein at least the minute needle is composed of a biodegradable resin and formed so as to be able to be injected an administering drug in the hollow center of axle portion, or is composed of a mixture of a biodegradable resin and an administering drug and formed so as to be a hollow shape or a solid-core shape. Further, in the present invention, the pad base may be those in which an administering drug is injected in a hollow center of an axle portion of the minute needle. Further, it may be utilized as a tube for feeding an administering drug. The minute needle which is installed upright from the patch base is not limited to one, but may be more than one.

As one mode of the minute needle in the pad base for endermism, a minute needle in which the edge is a tubular article made of a biodegradable resin and a drug can be injected in the tube is proposed. When it is used, the minute needle sting the skin by pasting the pad base for endermism on the skin and a drug in the minute needle is administrated in the skin. Further, even if the minute needle fractures and remains in the skin, since the minute needle is made of the biodegradable resin, it is decomposed in vivo and bad influence is hardly exercised to organism. Further, the above-mentioned tubular minute needle may be composed of a biodegradable resin and an administering drug. In this case, since the minute needle itself is dissolved (decomposed) in organism, a drug is also administrated thereby.

Further, as the mode of the minute needle, those in which both ends

are closed and a drug is sealed in the tube may be preferable. Since the minute needle is decomposed in organism, the drug sealed is discharged. In this case, the minute needle is not only composed of a biodegradable resin, but also it may be composed of a biodegradable resin and an administering drug.

Alternatively, the minute needle composed of a biodegradable resin and an administering drug may be a solid-core needle article, and medicinal benefits may be designed to be exhibited by a drug which is eluted from the minute needle itself, without involving the drug.

Further, the administration condition of a drug such as instantaneous effect and time-release property can be also changed by variously selecting the content form of a drug in the minute needle from among those in which a drug is sealed, those in which a drug is injected in a tube whose one end is opened, those in which a drug is kneaded in the biodegradable resin of the minute needle itself, and the like.

Further, according to the pad base for endermism using the pad base of the present invention, as described above, percutaneous absorption can be carried out only by pasting the pad on the skin, not depending on a medication procedure by vibration. Consequently, a power source for vibration and the like is unnecessary and it is more convenient.

Further, as the biodegradable resin, polylactic acid, polyethylene succinate, polybutylene succinate-adipate, polybutylene succinate-carbonate, polycaprolactone, polyester amide, polyester carbonate, polyvinyl alcohol, polyhydroxybutylate, mantriose, cellulose, cellulose acetate, collagen and mixtures of two or more kinds of these resins are recommended . In

particular, polylactic acid or copolymer of lactic acid with glycolic acid is preferable. For example, copolymer of lactic acid with glycolic acid, which has been already used as medical drugs, is gradually hydrolyzed in tissue to be lactic acid and gradually disappears.

Further, the above-mentioned administering drug may be either of liquid, cream, gel, suspension liquid and powder, and is not substantially limited excluding a drug not suitable for percutaneous administration.

The minute needle having a mixture of a biodegradable resin and an administering drug may be prepared, for example, by kneading the drug in the biodegradable resin and hardening it. Further, the administering drug which is mixed with the biodegradable resin does not always need to be the same as the administering drug which is injected in the above-mentioned hollow portion. For example, a drug which is easily mixed (hardly separated from the biodegradable resin) with the biodegradable resin while exhibiting the same medicinal benefits as the administering drug in the hollow portion may be used.

The minute needle of the present invention as described above may remain in the skin by positively folding this after being stung in the skin. When the minute needle is buried in the skin, the main body of the pad base for endermism is not peeled and medication is not interrupted; therefore a drug can be sustainably released for a long period of time.

As the size of the minute needle, it is preferable that an outer diameter is 20 μm or more and 500 μm or less, an inner diameter is 10 μm or more and 490 μm or less, and a length is 100 μm or more and 1 mm or less.

Further, the minute needle and the patch base may be integrally

formed from the same material. In this case, even if the patch base is pasted on the fractured minute needle, the patch base is also decomposed by organism because it is made of a biodegradable resin or a biodegradable resin and an administering drug; therefore, bad influence is hardly exercised.

Further, the injection needle of the present invention is characterized in that at least the needle portion of the injection needle is composed of a biodegradable resin or composed of a mixture of a biodegradable resin and an administering drug.

Similar to above description, even if the needle portion of the injection needle fractures and remains in the skin, the needle portion is decomposed in vivo because it is made of a biodegradable resin or a biodegradable resin and an administering drug; therefore, bad influence is hardly exercised to organism.

As the biodegradable resin used for the injection needle, those similar to above description can be used, and in particular, polylactic acid or a copolymer of lactic acid with glycolic acid is preferably.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a sectional view for illustrating the shape of the hollow portion of the minute needle in the pad base for endermism of the present invention;

FIG. 2 is a view showing the pad base for endermism of an embodiment of the present invention;

FIG. 3 A is the microscopic photograph of the minute needle in the

pad base for endermism of Example 10; and FIG. 3 B is a schematic view thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

The pad base for endermism of the present invention and the production process thereof are specifically illustrated below referring the drawings showing examples, but the present invention is not limited to the examples illustrated. It can be also carried out by appropriately adding modifications within a range adaptable in the purport described above and later, and any of them is included in the technical scope of the present invention.

FIG. 2A and FIG. 2B are views showing a pad base for endermism of one embodiment of the present invention, and FIG. 2 A is a sectional view thereof and FIG. 2 B is an upper view. Further, the upper side in FIG. 2 A is a patch face to the skin. The pad base for endermism includes a pad covered with a pressure-sensitive adhesive sheet from the reverse of skin side (the lower side in FIG. 2 A) of the above-mentioned pad base and is used by pasting it on the skin by the adhesion owing to the effect of the pressure-sensitive adhesive sheet. Alternatively, a drug is occasionally administered by compressing the needle to stick the skin without adhesive agent.

As shown in FIG. 2, numerous minute needles 1 are installed upright on a patch base 2. The minute needles 1 are a cylindrical member with a bottom in which a skin face side is opened. In the embodiment, both of the minute needles 1 and the patch base 2 are composed of a biodegradable resin

(for example, polylactic acid). It is preferable that the minute needles 1 and the patch base 2 are produced by integral molding.

A drug is filled in a hollow portion 3 of the minute needle 1 by suction from a drug container. When the pad base for endermism is used, it is pasted on the skin, the minute needles 1sting an organism by pressuring the patch base 2 and the drug in the hollow portions 3 is injected from the edges of the minute needles 1 in the organism.

As the shape of the minute needle 1, the minute needles 1 whose outer wall spreads and is thickened toward the patch base 2 are shown in FIG. 2, but they are not limited to this and the outer wall may be straight line.

In addition, the depth of the hollow portions 3 of the minute needles 1 may be deeper than those shown in FIG. 2. Concretely, as shown in FIG. 1 B [sectional views for illustrating the form of the hollow portions of the minute needles], there may be those in which the height H of the minute needles 1 is the same as the depth L of the hollow portions 3 [H = L (wholly hollow type: TYPE 2)], those in which the hollow portion 3 reaches on way to the thickness h of the patch base 2 as shown in FIG. 1 C [$H < L < H + h$ (semi-penetration type: TYPE 3)], and those in which the hollow portion 3 penetrate the patch base 2 as shown in FIG. 1 D [$H + h = L$ (whole penetration type: TYPE 4)]. Further, as shown in FIG. 1 A, those in FIG. 2 are one in which the depth L of the hollow portion 3 is shallower than the height H of the minute needles 1 [H>L (semi-hollow type: TYPE 1)]. It is hard to define a boundary clearly dividing the minute needles 1 and the supporting portion 2, in which the minute needles 1 and the patch base 2

were integrally molded, but here at, curvature shall be deemed as infinite, that is, a planar portion shall be deemed as a boundary plane, a portion below the plane or less shall be deemed as the patch base 2, and a portion installed upright from this is called as the minute needles 1.

The depth of the hollow portion 3 of each of the minute needles 1 in the pad base equipped with a plural number of the minute needles 1 may be wholly the same, or those having different depths may be used in combination. Further, as shown in the above-mentioned TYPE 4 (FIG.1 D), when the hollow portions 3 are those which penetrate the patch base 2 from the minute needles 1, a drug storing vessel is provided at the reverse of skin side of the patch base 2, and a drug may be fed to continuously carry out the administration of a drug.

According to the pad base for endermism of the present invention, even if the minute needles fracture and remain in the skin, they are decomposed by organism and hardly exercise bad influence. Further, after the minute needles sting the skin, they can be also used by positively folding the minute needles. Further, when the pad base for endermism is used, a drug can be administered without carrying out vibration as in a conventional MicroPatch method. Consequently, a power source and the like are unnecessary and medication can be easily carried out.

Further, as the injection needle of one embodiment of the present invention, the needle portion is composed of a biodegradable resin (for example, polylactic acid). The shape of the above-mentioned needle portion is similar to a usual injection needle and a thin needle is recommended from the viewpoint of the mitigation of pain.

In the injection needle of the present invention, even if the needle portion remains in the skin, it is also decomposed by organism and hardly exercises bad influence.

EXAMPLES

The pad bases for endermism of Examples of the present invention are illustrated below together with examples of the specific production process.

<Examples 1 to 3>

As a section bar for molding the minute needles, a section bar in which stainless steel wires (thin metal wires) having a length of about 30 mm and a diameter ϕ of 280 μm were vertically inserted by 5 wires in longitudinal and by 6 wires in a reticular pattern at an interval of 2 mm in a rubber plate was prepared. Then, the edges of stainless steel wires of the above-mentioned section bar were perpendicularly brought in contact with the bottom of a stainless steel dish and, 3 ml of a chloroform solution containing polylactic acid with a molecular weight of 101700 was poured in the stainless steel dish. After that, these were left alone, chloroform was evaporated by naturally drying and the polylactic acid was solidified. Then, the stainless steel wires were taken out from the stainless steel dish to obtain a pad base for endermism. Further, solutions with 5, 6 and 7% by weight as the concentration of polylactic acid in the above-mentioned chloroform solution containing polylactic acid were prepared, and pad bases which were obtained for the respective solutions were referred to as

Examples 1, 2 and 3.

Any of the above-mentioned Examples 1 to 3 was a pad base for endermism which had a plural number of the minute needles with a shape as shown in FIG. 1 D.

<Examples 4 to 6>

A similar section bar of the minute needles as the above-mentioned Examples 1 to 3 was used and the edges of stainless steel wires of the above-mentioned section bar were perpendicularly brought in contact with the bottom of a stainless steel dish. 3 ml of a chloroform solution containing polylactic acid with a molecular weight of 67400 was poured in the stainless steel dish, left alone, and the polylactic acid was solidified by natural drying. Then, the stainless steel wires were taken out from the stainless steel dish to obtain a pad base for endermism. Further, solutions with 10, 11 and 12% by weight as the concentration of polylactic acid in the above-mentioned chloroform solution containing polylactic acid were prepared, and pad bases which were obtained for the respective solutions were referred to as Examples 4, 5 and 6.

Any of the above-mentioned Examples 4 to 6 was a pad base for endermism which had a plural number of the minute needles with a shape as shown in FIG. 1 D.

<Examples 7 to 9>

A similar section bar of the minute needles as the above-mentioned Examples 1 to 3 was used and the edges of stainless steel wires of the section

bar were perpendicularly brought in contact with the bottom of a stainless steel dish. 3 ml of a chloroform solution containing polylactic acid with a molecular weight of 258700 was poured in the stainless steel dish, left alone, and the polylactic acid was solidified by natural drying. Then, the stainless steel wires were taken out from the stainless steel dish to obtain a pad base for endermism. Further, solutions with 1, 2 and 3% by weight as the concentration of polylactic acid in the above-mentioned chloroform solution containing polylactic acid were prepared, and pad bases which were obtained for the respective solutions were referred to as Examples 7, 8 and 9.

Any of the above-mentioned Examples 7 to 9 was a pad base for endermism which had a plural number of the minute needles with a shape as shown in FIG. 1 D.

<Examples 10 to 12>

A similar section bar of the minute needles as the above-mentioned Examples 1 to 3 was used, and the edges of stainless steel wires of the above-mentioned section bar were arranged so as to perpendicularly stand against the bottom while providing a little space from the bottom face of a stainless steel dish. To a chloroform solution containing polylactic acid with a molecular weight of 101700 (high molecular weight PLA) was added polylactic acid with a molecular weight of 10000 (low molecular weight PLA) in an amount of 0.1 part by weight based on the above-mentioned high molecular weight PLA, 3 ml of the mix solution was poured in the above-mentioned stainless steel dish, left alone so that one side ends of the stainless steel wires were immersed, and the polylactic acid was solidified by

natural drying. Then, the stainless steel wires were taken out from the stainless steel dish to obtain a pad base for endermism. Further, solutions with 5, 6 and 7% by weight as the concentration of polylactic acid in the chloroform solution of the above-mentioned high molecular weight PLA were prepared, and pad bases which were obtained for the respective solutions were referred to as Examples 10, 11 and 12.

Any of the above-mentioned Examples 10 to 12 was a pad base for endermism which had a plural number of the minute needles with a shape as shown in FIG. 1 C. The microscopic photograph (a magnification constant of 40-fold) of the minute needle in Example 10 obtained is shown in FIG. 3 A. Further, its schematic view is shown in FIG. 3 B.

<Examples 13 to 15>

A similar section bar of the minute needles as the above-mentioned Examples 1 to 3 was used, and the edges of stainless steel wires of the above-mentioned section bar were arranged so as to perpendicularly stand while providing a gap against the bottom of a stainless steel dish. Polylactic acid with a molecular weight of 10000 (low molecular weight PLA)in an amount of 0.1 part by weight based on the above-mentioned high molecular weight PLA was added to a chloroform solution containing polylactic acid with a molecular weight of 67400 (high molecular weight PLA), 3 ml of the mix solution was injected in the above-mentioned stainless steel dish, one side ends of the stainless steel wires were immersed in the solution, and the solution was raised on the surface of the stainless steel wires, left alone, and the polylactic acid was solidified by natural drying. Then, the stainless

steel wires were drawn out and taken out from the stainless steel dish to obtain a pad base for endermism. Further, solutions with 10, 11 and 12% by weight as the concentration of polylactic acid in the chloroform solution of the above-mentioned high molecular weight PLA were prepared, and pad bases which were obtained for the respective solutions were referred to as Examples 13, 14 and 15.

Any of the above-mentioned Examples 13 to 15 was a pad base for endermism which had a plural number of the minute needles with a shape as shown in FIG. 1 C.

<Examples 16 to 18>

A similar section bar of the minute needles as the above-mentioned Examples 1 to 3 was used, and the edges of stainless steel wires of the above-mentioned section bar were arranged so as to perpendicularly stand while providing a gap against the bottom of a stainless steel dish. To a chloroform solution containing polylactic acid with a molecular weight of 258700 (high molecular weight PLA) was added polylactic acid with a molecular weight of 10000 (low molecular weight PLA) in an amount of 0.1 part by weight based on the above-mentioned high molecular weight PLA, 3 ml of the mix solution was injected in the above-mentioned stainless steel dish, one side ends of the stainless steel wires were immersed in the solution, the solution was raised on the surface of the stainless steel wires, left alone, and the polylactic acid was solidified by natural drying. Then, the stainless steel wires were drawn out and taken out from the stainless steel dish to obtain a pad base for endermism. Further, solutions with 1, 2 and 3% by

weight as the concentration of polylactic acid in the chloroform solution of the above-mentioned high molecular weight PLA were prepared, and pad bases which were obtained for the respective solutions were referred to as Examples 16, 17 and 18.

Any of the above-mentioned Examples 16 to 18 was a pad base for endermism which had a plural number of the minute needles with a shape as shown in FIG. 1 C.

Further, the results of Examples 1 to 9 and the results of Examples 10 to 18 are summarized in Table 1 and Table 2, respectively.

Table 1

	Molecular weight of polylactic acid	Concentration of PLA (% by weight)
Example 1	101,700	5
Example 2	101,700	6
Example 3	101,700	7
Example 4	67,400	10
Example 5	67,400	11
Example 6	67,400	12
Example 7	258,700	1
Example 8	258,700	2
Example 9	258,700	3

Table 2

	Molecular weight of high molecular weight PLA	Concentration of high molecular weight PLA (% by weight)
Example 10	101,700	5
Example 11	101,700	6
Example 12	101,700	7
Example 13	67,400	10
Example 14	67,400	11
Example 15	67,400	12
Example 16	258,700	1
Example 17	258,700	2
Example 18	258,700	3

Since either of the pad bases (the patch base and the minute needles) of the above-mentioned Examples 1 to 18 is composed of polylactic acid, even if the minute needles fracture at usage and remain in the skin, they are anticipated to be biodegraded.

Examples 1 to 3 and 10 to 12 are more preferable among the above-mentioned respective Examples from the viewpoints of the adhering amount of polylactic acid to the stainless steel wires, the quality of membrane, and the easiness of pulling-out of the stainless steel wires.